Antibiotic prescribing for acute respiratory tract infections 12 months after communication and CRP training : a randomized trial

Title: Antibiotic prescribing for acute lower respiratory tract infections (LRTI) 12 months after internet-based training in communication skills and using CRP: a multi-national randomised trial

Authors: Paul Little, Beth Stuart, Nick Francis, Elaine Douglas, Sarah Tonkin-Crine, Sibyl Anthierens, Jochen W.L. Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris C. Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, Gilly O'Reilly, Alike van der Velden, Adam W.A. Geraghty, Herman Goossens, Theo Verheij, and Lucy Yardley on behalf of the GRACE consortium.

Professor Paul Little FRCGP, Professor Mark Mullee MSc, Dr Beth Stuart PhD, Dr Gilly O'Reilly PhD and Professor Michael Moore FRCGP, Dr Adam W.A.Geraghty PhD, Professor Miriam Santer PhD, Primary Care and Population Sciences Unit, University of Southampton, UK

Professor LucyYardley PhD, and Ms Elaine Douglas, MSc, Department of Psychology, University of Southampton, UK and Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Theo J.Verheij, PhD MRCGP and Dr Alike van der Velden PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands.

Professor Christopher C Butler FRCGP, Dr Sarah Tonkin-Crine PhD, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Nick Francis PhD, Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK.

Professor Kerenza Hood PhD, and Mr Mark Kelly PhD, South East Wales Trials Unit, Centre for Trials Research, Cardiff University

Professor Maciek Godycki-Cwirko MD Ph Hab. , Centre for Family and Community Medicine, Faculty of Health Sciences, Medical University of Łódź, Poland.

Associate Professor Artur Mierzecki, PhD Laboratory of Family Physician Education, Pomeranian Medical University in Szczecin, Poland.

Ms Mel Davies BSc Research Manager, Ely Bridge Surgery, Ely, Cardiff, UK.

Professor Antoni Torres, PhD Pneumology Department, Clinic Institute of Thorax (ICT), Hospital Clinic of Barcelona- Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)- University of Barcelona (UB)- Ciber de Enfermedades Respiratorias (Ciberes) Villarroel 170, 08036 Barcelona, Spain.

Professor Samuel Coenen, PhD, Department of Primary and Interdisciplinary Care (ELIZA), Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium.

Professor Herman Goossens, PhD, Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium.

Dr Sibyl Anthierens, PhD Department of Primary and Interdisciplinary Care (ELIZA), University of Antwerp, Belgium

Dr Carl Llor, PhD University Rovira i Virgili, Tarragona, Spain. Spanish Society of Family Medicine (semFYC).

Dr Jochen W.L. Cals, Maastricht University/CAPHRI, Maastricht, The Netherlands

Professor Hasse Melbye, PhD, University of Tromso, Norway

Word count 2374.Correspondence to Professor Little p.little@soton.ac.uk Tel +44 23 8059 1759 ; fax +44 2361 701125.University of Southampton. Aldermoor Health Centre, Aldermoor close, Southampton UK. SO16 5ST.

Abstract

Purpose. C-Reactive-Protein(CRP) has diagnostic utility for lower Respiratory infections (LRTI). A large international trial documented that training in communication skills, CRP, or both, reduced antibiotic prescribing at 3 months (risk ratios 0.68,0.53,0.38 respectively). We report the longer term impact.

Methods. 246 general practices in 6 countries were cluster-randomised using computer-generated random numbers to:

1) Usual care (n=61); Internet training for 2) CRP point-of-care-test (POCT) (n=62), or 3) enhanced communication skills and interactive booklet (n=61), or 4) combined interventions (n=62). Outcome: antibiotic prescribing audited for RTIs after 12 months(12m).

Results. Of 228 practices providing 3m data 168 (74%) provided 12m data (n=40,39,41,48 respectively) with no demonstrable attrition bias. Prescribing had reduced in usual care (3m 58%(508/870); 12m 51%(613/1194)), but increased for the CRP (3m 35%(368/1062), 12m 43%(456/1052); adjusted RR (Risk Ratio) compared to usual care 0.75 (95% CIs 0.51,1.00), p=0.052) and combined groups (3m 32%(476/1170), 12m 45% (641/1410), RR 0.70 (0.49,0.93), p=0.013). However, reductions for communication training were maintained (3m 41%(476/1170), 12m 40%(465/1166), RR 12m 0.70 (0.49,0.94), p=0.017). Despite being freely provided, CRP POCT was hardly used at 12m, and booklets used sparingly. Enhanced communication, but not CRP, remained effective for Lower RTIs (RRs 0.71, 0.45 to 0.99; and 0.76, 0.47 to 1.06) respectively), whereas both remained effective for Upper RTIs (0.60; 0.37 to 0.94 p=0.023; 0.58 0.36 to 0.92; 0.018).

Conclusion. Internet-based training in enhanced communication skills remains effective in the longer term. The effect of CRP training wanes and becomes ineffective for LRTI, the only current indication for using CRP.

Funding: EuropeanCommissionFrameworkProgramme6; UK NIHR; ResearchFoundation–Flanders(G.0274.08N); European Science Foundation; **Trial Registration:**ISRCTN99871214

Introduction

Acute uncomplicated lower (LRTI) and upper (URTI) respiratory tract infections are the most common acute presentations in primary care, and most patients still receive antibiotics [1 2 3 4] despite evidence of limited benefit[5 4 6]. Antibiotic resistance is a major threat and primary care prescribing has a key role[7].

Educational outreach and training in enhanced communication skills for physicians to explore patients' concerns can reduce antibiotic prescribing[8-13]. Particular concerns for physicians and patients are complications such as pneumonia[14 15] where LRTI C-Reaction-Protein (CRP) point-of-care-tests (POCT) have diagnostic utility[16]. Physician training for CRP POCTs reduces antibiotic prescribing by approximately 20%[8 9] in the short term, so several guidelines now advocate CRP (e.g. European Respiratory Society(ERS); European Society Clinical Microbiology and Infectious Diseases(ESCMID); National Institute for Health and Care Excellence (NICE)) [17 18 19].

Evidence for educational outreach mostly documents highly expert teams helping a small numbers of practices i.e. of limited generalisability. However, a large pan-European trial documented the impact of brief internet-based physician training by: 1) using a CRP POCT and; 2) enhanced communication skills and using an interactive patient booklet. There was a clinically unimportant increase of one day of symptoms (a secondary outcome, documented in a symptom diary) [20], but both interventions reduced antibiotic prescribing (the primary outcome) by 3 months (risk ratio (RR) 0.53 and 0.68 respectively; combined intervention 0.38)[20]. It is unclear if either of these brief interventions has longer lasting effects on antibiotic use - which is vital to curb the danger of antibiotic resistance. We report the impact of the interventions after 12 months.

Methods

The methods of this trial are given in greater detail elsewhere[20]. A summary is included below.

Rationale of trial design

A cluster design was chosen to minimise contamination within practices.

Changes following trial commencement

Funding uncertainty meant asking participating physicians for the 12 month audit only after completing the 3 month audit. Clinical outcomes were not documented at 12 months – due to resource limitations and also minimal impact at 3 months[16]. At 3 months there were no significant differences between groups in hospital admissions (2 control; 10 CRP; 6 Communication; 12 Combined - mostly cardio-respiratory, or systemic upset (e.g. high fever)).

Participating networks, physician practices, and audits

Eight primary care research networks invited local physician practices. Networks covered a range of health systems, languages and cultures: England (Southampton); Wales (Cardiff); Netherlands (Utrecht); Belgium (Antwerp); Poland (Łódź; Szczecin); and Spain (Barcelona; the SemFYC network).. Within each practice, all who prescribed antibiotics for RTI could participate (including some UK nurse prescribers).

- Baseline audit of consecutive participants to document usual prescribing : October -December 2010
- 3 month audit[20]: February -May 2011; physicians were asked to recruit 30 consecutive patients with LRTI (the main intervention target) and 5 URTIs.
- 12 month audit: October 2011-May 2012; since the interventions were effective for both LRTI/URTI at 3 months[20], both LRTI and URTI were included with no instructions to preferentially recruit LRTI.

Inclusion criteria for practices: no prior participation in antibiotic stewardship interventions; able to recruit 10+ patients at baseline.

Patients

Inclusion criteria. Adults (>=18 years old) with**:**

LRTI*:* <= 28 days of cough as the most prominent symptom, or if not (e.g. chills prominent) the clinician judged LRTI was the diagnosis. Pneumonia and chronic airways disease were included since their management could have been modified by the interventions.

URTI: judged by the clinician to be another RTI (sore throat, otitis media, sinusitis, influenza and/or coryzal illness).

Exclusions: non-infective diagnosis (e.g. pulmonary embolus); recent antibiotic (28 days); informed consent impossible (e.g. dementia); pregnancy; immune deficiencies.

Case report form (CRF): clinicians documented symptoms and signs, illness duration, the use of: CRP booklets, and antibiotic prescribing.

Randomisation

Remote randomisation of practices used minimisation based on practice characteristics (baseline prescribing; number of physicians; number of patients at baseline), stratified by network.

Intervention

The two interventions (enhanced communication; CRP) were developed to be sensitive to cultural differences [21] whilst retaining core features. Practices were randomised to one of four trial arms:

1. **Usual care**. No intervention provided.
2. **CRP: Internet training to use a CRP POCT.** The POCT device was demonstrated by company representatives; internet training provided guidance on targeting CRP use (Appendix 1). The device and testing materials were provided free.
3. **Internet based training in enhanced communication skills and using an interactive patient booklet** (see Appendix1). The internet training focused on interactive use of a booklet in consultations and enhanced patient-centred communication - eliciting concerns/expectations, information exchange, agreeing management, summing up, and safety netting – supported by short demonstration video clips. The booklets included information about the cause of symptoms; natural

history; antibiotics; self-help and when to re-consult. Group practices appointed a lead physician to organise a structured meeting on prescribing.

4. **Combined intervention.** Physicians received both training interventions.

Outcomes

Primary outcome: antibiotic prescribing documented in the CRF by the recruiting clinician. There was no individual level consent for data collection at 12 months. Limited availability of prescription monitoring prevented pharmacy dispensing data being used.

Sample size calculation (for alpha 0.025; beta 0.2)

We assumed: 30 patients/practice would be recruited; antibiotic prescribing reductions of 50% to 40% for either intervention [8 22]; an intra-cluster coefficient (ICC) from 0.16 ([8 23 24]) to 0.06[25]. Hence we required 2600 (ICC 0.06) to 5400 patients (ICC 0.16).

Analysis

Multilevel logistic regression modelling for a factorial study was used, controlling for baseline antibiotic prescribing rate, clustering by physician and practice, whether a URTI or LRTI, and a range of potential confounders (see bottom of Tables 2,3). There was no additional effect of international network hence it was not included in models. A secondary analysis reported individual randomisation groups since the study was not powered for interactions. The odds ratios were converted to risk ratios (Zhang et al [26]). The analysis was intention-to-treat. To assess attrition bias we performed two analyses: 1) using data aggregated at the practice level, and using multiple imputation to impute data from practices who had not agreed to be followed-up 2) comparison of estimates at 3 months just for those practices followed up at 12 months.

Results

At the baseline audit 5355 patients (79.1%) had LRTI, and 1416 (20.9%) URTI, of whom 3742 (55%) were prescribed antibiotics. 372 participating physicians in 228 of 246 practices contributed 4264 patients at the 3 month follow-up (see Figure1) of whom 20% had URTI. Of 228 practices providing 3 month data 168 (74%) provided 12 month data. 247 physicians in the 168 practices contributed 4830 patients at the 12 month follow-up and 41% of patients had URTI, hence URTI was controlled for in the estimates. Groups were well balanced and remained so (Table 1). Initial compliance with training was good, with high completion of all modules (CRP 99/113 (88%); Communication 94/108(87%); Combined 116/127 (91%)).

By 12 months CRP was little used despite free access to CRP diagnostic kits: Usual care16/1195 (1.34%), CRP 62/1075 (5.77%) Communication 56/1168 (4.79%), Combined 85/1419 (5.99%). Booklets were used more sparingly too: Communication 189/1186 (16%); Combined 340/1428 (24%)).

Main findings (Tables 2 and 3)

Factorial analysis.

At 3 months 48% (984/2040) of participants consulting physicians who were not trained in using CRP were prescribed antibiotics and by 12 months 46% (1078/2360). At 3 months antibiotic prescription in the CRP groups was 33% (734/2224) but by 12 months it was 45% (1097/2462); adjusted risk ratio 0.87 compared to control (95% confidence intervals 0.68 to 1.06, p=0.181). At 3 months 45% (876/1932) of participants not in Communication skills groups had antibiotics prescribed, and similar at 12 months (48% (1069/2246). At 3 months 36% (842/2332) of participants in the Communcation skills groups had antibiotics prescribed and at 12 months 43% (1106/2576; adjusted risk ratio compared with control 0.81, 0.64 to 1.00, p=0.049).

Analysis of individual groups

The factorial analysis probably masks the effectiveness of individual interventions, since there was a sizeable interaction term (1.67;p=0.155) between CRP and Communication interventions. The individual group results at 12 months are shown in Table 3. In those receiving usual care (i.e. no training) 58%

(508/870) were prescribed antibiotics at 3 months, and this had reduced by 7% to 51% (613/1194) at 12 months in part due to more URTI. However for CRP training figures reversed 35% (368/1062) at 3 months, rising by 9% to 43% (456/1052) at 12 months (adjusted risk ratio compared to usual care at 12 months 0.75, 0.51 to 1.00, p=0.052). Similarly for the combined group: 32% (476/1170) were prescribed antibiotics at 3months, rising by 13% to 45% (641/1410) at 12 months (adjusted risk ratio compared to usual care at 12 months 0.70 , 0.49 to 0.93, p=0.013). In contrast for Communucation skills 41% (476/1170) were prescribed antibiotics at 3 months, and maintained by 12 months (40%, adjusted risk ratio compared to usual care 0.70, 0.49 to 0.94, p=0.017). Enhanced communication was also still effective for LRTI (adjusted risk ratio 0.71, 0.45 to 0.99) but CRP was not (0.76, 0.47 to 1.06) whereas both interventions maintained an effect on URTI. (respectively 0.60; 0.37 to 0.94 p=0.023; 0.58 0.36 to 0.92; 0.018).

Attrition bias

Data from practices where follow-up was possible was comparable to the overall trial cohort (see Appendix 2 tables 5 and 6). The practice level analysis compared the results of the 'completers' analysis (from practices that agreed to follow-up) with the estimates based on including all practices in an imputed data set. Although the absolute estimates of effectiveness were slightly different with lower power and were less robust (due to the inability to control for individual patient characteristics), nevertheless no meaningful change in the practice-based estimates occurred when data from the missing practices was imputed. This suggests that minimal attrition bias operated due to practices not agreeing to the follow-up study (Table 4). As a further check the estimates at 3 months from just those practices who were followed-up at 12 months ('completers') were very similar to the whole trial cohort (3 months data for the 12 month 'completer' practices: CRP 0.54, communication training 0.68; full cohort: 0.54, 0.69 respectively).

Discussion

As far as we are aware, this is the first major multi-centre international trial to assess the longer term effectiveness of internet training to modify antibiotic prescribing for RTIs. Despite a reduction in antibiotic prescribing in usual care, communication training maintained effectiveness, but CRP training did not.

Potential Limitations

Practices were only approached after 3 months to request further follow-up, and 30% of practices declined. However, the baseline characteristics were similar in practices that were not followed up, and the practice-level analysis using multiple imputation demonstrated no attrition bias. Most practices approached agreed, many of whom had not previously taken part in research. As expected clinicians reported struggling to document consecutive patients at busy times of year, but previous research has shown this results in minimal selection bias[27 28]; there were also minimal barriers to participation for the follow-up (quick audit proformas; no delay for patient consent), there was no evidence of differential selection bias comparing groups, and analysis controlled for any differences in case mix. Furthermore, antibiotic prescribing was similar to previous studies[4 2], and most patients at baseline in usual care received antibiotics, which suggests generalisable results. At 12 months usual care prescribing reduced slightly by 6% - perhaps due to pressure on physicians (e.g. the European Antibiotic Awareness Day), but also there were more patients with URTI (which explained half the reduction). However the findings cannot be explained by case mix since we controlled for a range of variables in the analysis. We checked fidelity with initial training but didn't observe consultations (to avoid changing behaviour). We did not record clinical outcomes since given the modest impact initially[20].

Comparison with other studies

Interactive communication was effective in the longer term, supporting prior evidence for interactive methods[10 11]. Our process studies also indicated that the communication intervention promoted changes in physician attitudes that should be helpful in the longer-term [21 29 30]. STAR achieved a 4% reduction in global antibiotics but was more intensive (five online phases vs one in this study; expert-led outreach

seminars)[13]. Our intervention caused less initial reduction than the Dutch IMPAC3T trial [8], but IMPAC3T was also more intensive, with face-to-face communication training. The long-term effect on behaviour in the current study was similar to other more intensive interventions[8 13 31]. Booklets were initially important, but their limited use in follow-up - despite the intervention maintaining effectiveness - suggests that doctors had consolidated skills and were being more selective.

Communication skills-training was less slightly effective than using CRP, or the combined intervention at 3 months (risk ratios 0.68,0.53,0.38 respectively), comparable to the Dutch trials[8 9]. However, despite providing all materials free, CRP tests were little used by 12 months, and the effectiveness of CRP had waned substantially (0.70,0.75, 0.70 respectively) – but the reduced impact was particularly for LRTI where CRP is supported[17 18 19]. Our findings support the long term findings for LRTI from the smaller intensive IMPAC3T trial, where there was no longer a significant effect of CRP training but the effect of communication training remained[31]. The waning in effectiveness of CRP may reflect the waning of quality improvement interventions with time, and it is unclear if further reduction in effectiveness would happen beyond 12 months. The logistics of providing CRP, and time taken to do CRP at the busiest times of year may be key disincentives to longer term engagement. The ongoing impact of CRP training for URTI despite low use of CRP may reflect physicians having learnt to prescribe fewer antibiotics when using CRP, or that both CRP and Communication training shared introductory modules about the limited benefit of antibiotics i.e. a non-specific effect not related to CRP per se. Ongoing incentives would probably be needed for physicians to continue using CRP, but evidence of cost-effectiveness of this approach would be needed.

Conclusion

Internet-based training in enhanced communication skills remains effective in the longer term. The effect of CRP training wanes and becomes ineffective for LRTI, the only current indication for using CRP. In routine clinical practice there is only likely to be short term benefit from training GPs to use CRP. The most useful training for long lasting effects is in enhanced communication skills.

Acknowledgements and Contributorship.

The research performed by the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe) consortium leading to these results was funded by the European Community's Sixth Framework Programme under grant agreement no. 518226. The work in UK was also supported by the National Institute for Health Research (service support costs), and the Research Foundation –Flanders (G.0274.08N). The funders and sponsor (University of Southampton) had no role in the management, analysis, interpretation nor write-up of this project. We are grateful to Orion Diagnostica for supplying all the equipment and conusumables for CRP testing.

The work reported as part of the final follow-up was also supported through the European Science Foundation (ESF), in the framework of the Research Networking Programme TRACE (www.esf.org/trace) (whose contributors were *Bond University (Australia), Research Foundation – Flanders, University of Antwerp, University of Ghent (Belgium), Chinese University of Hong Kong (China), University of Copenhagen (Denmark), Research Council of Health, Academy of Finland (Finland), College Azuréen des Généralistes Enseignants, Comité Départemental d'Education pour la Santé (France), Rostock University (Germany), The Netherlands Organisation for Scientific Research, AMC Amsterdam, Leiden UMC, UMC Utrecht (The Netherlands), Research Council of Norway, University of Oslo, University of Tromso (Norway), Medical University of Bialystok, Medical University of Lodz (Poland), National University Research Council (Romania), Osnovno zdravstvo Gorenjske (Slovenia), l'Institut d'Investigacions Biomèdiques August Pi i Sunyer (Spain), Swedish Research Council, Karolinska Institute (Sweden), Medical Research Council, Cardiff University, University of Oxford, University of Southampton (United Kingdom), Swiss National Science Foundation (Switzerland)).*

The initial idea for this study was proposed by PL, TV, CCB, SC and HG; all authors contributed to the development of the protocol, and to the management of the study; Gilly O'Reilly and Curt Brugman led the day to day management of the study supervised by PL and TV respectively; LY led and supervised the design and development of the web-based intervention; LY, NF, PL, CCB led the development of the communication intervention. JC, HM and PL led the development of the CRP intervention. Both interventions benefited from input of the network leads. Frank Leus supervised the web based data management. HG led the funding application and provided overall coordination of the GRACE consortium; KH coordinated randomisation and MK; PL, BS and MMu analysed the data; all authors contributed to the interpretation of the data and the write up. PL, MMu and BS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. No authors have a conflict of interest.

We are grateful to Zoe Crosby and Ian Williamson (who have provided helpful support during the study, and were part of protocol development in discussion with PL). Key members of the GRACE consortium trial team whose hard work has made this possible are: Niels Adriaenssens, Zuzana Bielicka, Pascale Bruno, Jo Coast, Patricia Fernandez, Iris Hering, Anna Kowalczyk, Christina Lannering, Marieke Lemiengre, Katherine Loens, Christine Lammens, Greet Ieven , Bo-Eric Malmvall, Anna Kowalczyk, Jaroslaw Krawczyk , Nuria Sanchez Romano, Matteu Serra Prat,

Igor Svab, Richard Smith, Jackie Swain, Francesco Blasi, Ann de Sutter, Pia Touboul, Tom Schaberg, Sigvard Molstad, Paolo Tarsia, Helena Hupkova, Janko Kersnik, Frank Leus, Robert Veen, Tricia Worby, Ana Moragas, Josep Maria Cots, Javier Arranz, Guillermo García, Gloria Rabanaque, and Juande Alcántara.. We are very grateful to all the clinicians and patients who consented to be part of GRACE, without whom this study would simply not have been possible. We would also like to thank the independent GRACE trial steering committee for their help and suggestions (Patrick Bindels, Gordon Taylor, and Mark Woodhead). The trial steering committee also supervised safety aspects of the trial since there was no independent data safety monitoring board (following similar precedents with low risk MRC funded trials, as the study was considered to be low risk).

Approvals.

Ethical approval for the UK was granted by Southampton and South West Hampshire Local Research Ethics Committee for: Genomics to combat Resistance against Antibiotics for Community acquired lower respiratory tract infection (LRTI) in Europe: INternet Training for Reducing antibiOtic use trial (Short title: GRACE INTRO Trial REC Ref 10/H0502/29). The research sites outside of the UK also obtained ethical approval from their local organisations. Patients who fulfilled the inclusion criteria were given written and verbal information about the study and asked for informed consent.

Funder/author role.

The funders had no role in study management, analysis, write-up or the decision to publish. The PI (PL) made the decision to submit for publication following agreement from all authors.

References

1. Akkerman E, Van der Wouden J, Kuyvenhoven M, et al. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *Journal of Antimicrobial chemotherapy* 2004;54:1116-21.
2. Petersen I, Johnson A, Islam A, et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007;335:982 (10 November), doi:10.1136/bmj.39345.405243.BE.
3. Kroening-Roche J, Soroudi A, Castillo E, et al. Antibiotic and bronchodilator prescribing for acute bronchitis in the emergency department. *J Emerg Med* 2012;43:221-27.
4. Butler C, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009;b2242
5. Smith S, Fahey T, Smucny J, et al. Antibiotics for acute bronchitis. *Cochrane Library* 2014;DOI: 10.1002/14651858.CD000245.pub3
6. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower respiratory tract infection where pneumonia is not suspected clinically : a 12 country randomised placebo controlled trial in primary care. *Lancet Infectious Disease* 2013;Feb;13(2):123-9. doi: 10.1016/S1473-3099(12)70300-6.
7. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
8. Cals J, Butler C, Hopstaken R, et al. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009;doi:10.1136/bmj.b1374
9. Cals J, Schot M, de Jong S, et al. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010;8(124):133.
10. Arnold S, Straus S. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database of systematic reviews* 2005
11. O'Brien M, Rogers S, Jamtvendt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database of systematic reviews* 2007
12. van der Velden A, Pijpers E, Kuyvenhoven M, et al. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. *BJGP* 2012;62:e801-e07(7).
13. Butler C, Simpson S, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012;344:d8173. doi: 10.1136/bmj.d8173.
14. Kumar S, Little P, Britten N. Why do Gps prescribe antibiotics for sore throat? A grounded theory interview study of general practitioners. *BMJ* 2003;326:(18 January):138.
15. Cornford CS. Why patients consult when they cough: a comparison of consulting and non-consulting patients. *BJGP* 1998;48:1751-54.
16. Minnaard MC, de Groot JA, Hopstaken RM, et al. The added value of C-reactive protein measurement in diagnosing pneumonia in primary care: a meta-analysis of individual patient data. *Cmaj* 2016 doi: 10.1503/cmaj.151163 [published Online First: 2016/09/21]
17. NICE clinical guideline 191: Pneumonia Diagnosis and management of community- and

hospital-acquired pneumonia in adults. *NICE* 2014;191
18. Verheij T, Hopstaken R, Prins Jea. NHG-Standaard Acuut hoesten. [Dutch College of General Practitioners Guidelines on Acute Cough 2011, updated 2013]. *Huisarts Wet* 2011;54:68-92.
19. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* 2011;17 Suppl 6:E1-E59.
20. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013;doi:10.1016/S0140-6736(13)60994-0
21. Anthierens S, Tonkin-Crine S, Douglas E, et al. General practitioners' views on the acceptability and applicability of aweb-based intervention to reduce antibiotic prescribing for acute cough in
multiple European countries: a qualitative study prior to a randomised trial. *BMC Fam Pract* 2012;13:101:doi:10.1186/471-2296-13-101.
22. Francis N, Butler C, Hood K, et al. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009;339:b2885.
23. Coenen S, Van Royen P, Michiels B, et al. Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. *J A C* 2004;54(3):661 (doi:10.1093/jac/dkh374)-672.
24. Welschen I, Kuyvenhoven M, Hoes A, et al. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. *BMJ* 2004;329:431 (21 August), doi:10.1136/bmj.38182.591238.EB.
25. Adams G, Gulliford M, Ukoumunne O, et al. Patterns of intra-cluster correlation from primary care research to inform study design and analysis. *J Clin Epidemiol 2004 Aug;57(8):785-94* 2004;57:785-94.
26. Zhang J, Yu K. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-91.
27. Little PS, Williamson I, Warner G, et al. An open randomised trial of prescribing strategies for sore throat. *B M J* 1997;314:722-27.
28. Little P, Gould C, Williamson I, et al. A pragmatic randomised controlled trial of two prescribing strategies for acute otitis media. *BMJ* 2001;322:336-42.
29. Yardley L, Douglas E, Anthierens S, et al. Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled tria. *Implementation Science* 2013;8:134:doi:10.1186/748-5908-8-134.
30. Anthierens S, Tonkin-Crine S, Cals J, et al. Clinicians' Views and Experiences of Interventions to Enhance the Quality of Antibiotic Prescribing for Acute Respiratory Tract Infections. *JGIM* 2014;DOI 10.1007/s11606-014-3076-6
31. Cals J, De Bock L, Beckers P-J, et al. Enhanced Communication Skills and C-reactive Protein Point-of-Care Testing for Respiratory Tract Infection: 3.5-year Followup of a Cluster Randomized Trial. *Ann Fam Med* 2013;11 doi:10.1370/afm.1477.:157-64.
32. Yardley L, Joseph J, Michie S, et al. Evaluation of a Web-based intervention providing tailored advice for self-management of minor respiratory symptoms: exploratory randomized controlled trial. *J Med Internet Res* 2010;12:e66.

33. van der Meer V, Neven AK, van den Broek PJ, et al. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005;331:26.
34. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. *Fam Pract* 2009;26:10-21.

425 Table 1 – Patient characteristics (n (%) or mean (SD))

	Final twelve months follow up				Initial three months follow-up period				Baseline
	Control for CRP	CRP	Control for comm'n	Communic'n	Control for CRP	CRP	Control for communic'n	Communicat'n	
Gender (female)	1,470/2,463 (60%)	1,620/2,699 (60%)	1,466/2,464 (60%)	1,624/2,698 (60%)	1311/2040 (64%)	1423/2224 (64%)	1223/1932 (63%)	1511/2332 (65%)	4218/6771 (62%)
Age in years (mean (SD))	51.7 (18.8)	51.2 (18.7)	51.1 (18.6)	51.7 (18.8)	50.9 (17.3)	51.0 (17.5)	50.8 (17.6)	51.1 (17.2)	49.6 (18.6)
Non-smoker (past or current)	N/A	N/A	N/A	N/A	1067/2040 (52%)	1147/2224 (52%)	1041/1932 (54%)	1173/2332 (50%)	N/A
Illness duration prior to the index consultation greater than 5 days	1,026/2,463 (42%)	1,198/2,699 (44%)	1,032/2,464 (42%)	1,192/2,698 (44%)	1038/2027 (51%)	1128/2209 (51%)	994/1917 (52%)	1172/2319 (51%)	3,542/6717 (53%)
Respiratory rate (greater than 25 breaths/minute)	65/2462 (3%)	133/2699 (5%)	96/2464 (4%)	102/2698 (4%)	101/1991 (5%)	123/2142 (6%)	145/1866 (8%)	79/2267 (3%)	N/A
Temperature (greater than 38 degrees C)	291/2463 (12%)	380/2699 (14%)	285/2464 (12%)	386/2698 (14%)	228/2002 (11%)	280/2152 (13%)	202/1853 (11%)	306/2301 (13%)	N/A

426
427
428

429

430

Table 2 - Effectiveness of CRP and enhanced-communication training in reducing antibiotic prescribing rates at 12 months

	No CRP training	CRP training	No communication training	Communication training
Crude percentage	45.7% (1,078/ 2,360)	44.6% (1,097/ 2,462)	47.6% (1,069/ 2,246)	42.9% (1,106/2,576)
Basic risk ratio (95% CI)*	1·00	0.91 (0.77, 1.05;p=0.223)	1·00	0.90 (0.77, 1.04; p=0.170)
Adjusted risk ratio†	1·00	0.87 (0.68, 1.06; p=0.181)	1·00	0.81 (0.64, 1.00; p=0.049)

CRP=C-reactive protein. *The basic model adjusted for baseline prescribing and clustering by physician and practice. †The adjusted model controlled for diagnosis (LRTI, URTI, pneumonia), sex, age, presence of cough, phlegm, shortness of breath, blocked/runny nose, chest pain, fever, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with social activities, earache, sore throat, facial/sinus pain, crackles, wheeze, pulse higher than 100 beats per min, temperature higher than 37·8°C, respiratory rate, physician's rating of severity, low blood pressure, duration of cough and duration of illness prior to consultation.

Table 3 - Effectiveness of CRP and enhanced-communication training in reducing antibiotic prescribing rates at 12 months

	Control	CRP	Enhanced communication	Combined
Crude percentage	51.3% (613/1,194)	43.4% (456/1,052)	39.9% (465/1,166)	45.5% (641/1,410)
Basic risk ratio (95% CI)*	1·00	0.83 (0.66, 1.02; p=0.083)	0.83 (0.66, 1.01; p=0.065)	0.83 (0.66, 1.00; p=0.053)
Adjusted risk ratio†	1·00	0.75 (0.51, 1.00; p=0.052)	0.70 (0.49, 0.94; p=0.017)	0.70 (0.49, 0.93; p=0.013)

CRP=C-reactive protein. *The basic model adjusted for baseline prescribing and clustering by physician and practice. †The fully adjusted model controlled for the variables listed above.

Table 4 - Effectiveness of CRP and enhanced-communication training in reducing antibiotic prescribing rates based on a practice level analysis compared 'complete case' percentages with estimates from an imputed dataset at 12 months

	Control	CRP	Enhanced communication	Combined
Complete case percentage	51.0%	42.9%	39.8%	47.1%
		-7% (-15, 2; p=0.113)	-7% (-15, 1; p=0.089)	-4 % (-12, 4; p=0.296)
Imputed	**Control**	**CRP**	**Enhanced communication**	**Combined**
*** % receiving antibiotic prescription**	49.7%	42.9%	41.9%	47.0%
		-6% (-14, 3; p=0.215)	-7% (-15, 1; p=0.100)	-4% (-12, 4; p=0.342)

* Reduction in proportion compared to control controlling for baseline prescribing and practice level averages of patient characteristics: age, type of infection (LRTI/URTI), presence of symptoms (listed above), crackles, wheeze, pulse higher than 100 beats per min, temperature higher than 37·8°C, respiratory rate, physician's rating of severity, and duration of cough

Appendix 1.

Development of enhanced communication skills and booklet intervention

We developed brief internet based training modules using LifeGuide software, using both prior theory and building on previous interventions: internet training and booklet-based format and content for sharing with patients [22 32] and the STAR model for communication training [13]. The materials were piloted in every country and modified according to feedback from interviews with physicians and patients in each country[21]. The booklet was endorsed by the European Antibiotic Awareness Day coordinated by the European Centre for Disease Prevention and Control. To reinforce the communication training group practices were asked to appoint a lead physician who organised a structured meeting where prescribing issues were discussed. The experience of using the patient booklet, and recent cases of LRTI were discussed (participants were asked to document presentation, management and their reflection on consultations for up to 10 recent cases). The pragmatic nature of this study required flexibility in arranging meetings: sometimes meetings in practices were not possible (for example with many single handed practices in Belgium, where meetings between practices were encouraged), and sometimes there was strong preference to have centrally organised meetings (e.g. Poland).

Development of CRP intervention

The text for guidance on the use of CRP was developed based on systematic review evidence[33 34]and the previous IMPAC3T trial[8] and led by Jochen Cals, Hasse Melbye and Paul Little with input from the network leads and collaborators.

GRACE INTRO web-based training module

The training modules consisted of up to three sections; an introduction (seen by Communication, CRP, and Combined groups) training in communication skills and use of a patient booklet (seen by Communication and Combined groups) and training in using a C-reactive protein point of care (CRP) test (seen by CRP and Combined groups).

1. Introduction

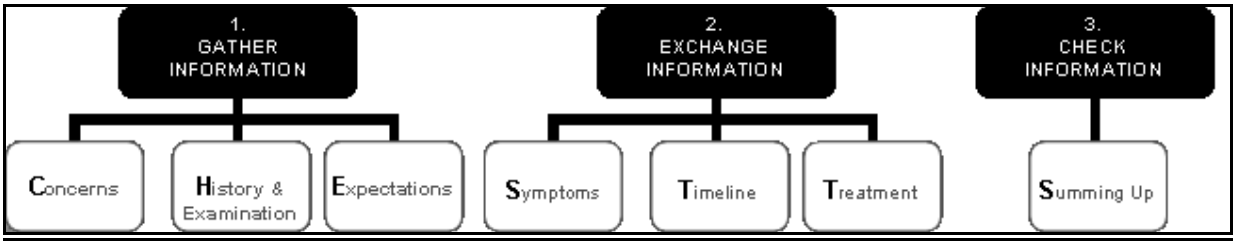
This section presented information describing the problem of antibiotic resistance for healthcare, its relation to antibiotic use, the medicalization of self-limiting illness creating the 'vicious circle' of encouraging re-consultation during subsequent episodes, and the difficulties in determining what patients presenting with LRTI in primary care may benefit from antibiotic treatment. The introduction discusses common concerns Physicians have when deciding whether or not to prescribe antibiotics and explains

how physician training in communication skills and/or physician use of CRP point of care testing could potentially assist in the consultation.

2. Enhanced Communication skills training and use of patient information booklet

The aim of the communication skills training was to facilitate physicians in using specific patient centred communication skills in the acute cough consultation, using three elements of an effective consultation: to gather information about patient beliefs and expectations, exchange information and agree management, and check patient understanding and concordance. Each of these has steps for the physician to follow (see Figure 1 below). The acronym of these seven steps is CHESTTS which helps ease of recollection in the English version of GRACE INTRO.

Furthermore, it was outlined how a patient booklet could be helpful in the consultation (with a focus on exchanging information and shared decision-making). The web pages presented information, backed by research evidence, to explain how a booklet could help to address patient concerns and maintain patient satisfaction. Physicians were encouraged to make use of tick boxes in the booklet to highlight specific sections which were relevant to individual patients in order to personalise the information. An online discussion forum was also provided for participating physicians but was used by relatively few.



A diagram showing the three elements of an effective consultation and the steps involved in each of these to be carried out by a GP.

The last section of the communication skills training presented eight short video clips to give examples of how each of the seven tasks above could be achieved in the consultation. For 'Treatment' two videos were displayed; one giving advice about the appropriate use of antibiotics and one video clip giving advice on self-management of acute cough. The video clips were shot in a physician office with a qualified physician giving advice to an actor playing the role of a patient with acute cough. The training ends with a page summarising the key points of communication skills training module.

3. C-Reactive Protein (CRP) point of care testing Training

The aim of the training in the use of point of care CRP was to inform physicians about how a point of care CRP result could assist in differentiating self-limiting from serious LRTI and making antibiotic prescribing decisions for LRTI. Physicians were shown how to interpret specific CRP values and how to use the test in their consultations.

The training starts by giving information on the background of CRP point of care testing and providing evidence to support its use in primary care for LRTI. Physicians were encouraged to use the test to differentiate between serious and self-limiting LRTIs. Common misconceptions were discussed. The module stresses that the test cannot distinguish between viral and bacterial infections in primary care and that it is not a stand-alone test, but should always be used alongside history taking and a physical examination.

Relevant cut off points were provided (see Table below). As part of dealing with values in the intermediate range (CRP 20-100 mg/l) delayed prescribing was discussed and presented as an option if illness severity combined with CRP did not warrant immediate antibiotics.

<u>Guidance available to physicians on the cut off points used for CRP values and the relevant treatment options.</u>

CRP ≤ 20 mg/l
▪ Self-limiting LRTI ▪ Withhold antibiotics
CRP 21-50 mg/l
▪ Majority of patients have self-limiting LRTI ▪ Assessment of signs, symptoms, risk factors and CRP is important ▪ Withhold antibiotics, in most cases
CRP 51-99 mg/l
▪ Assessment of signs, symptoms, risk factors and CRP is crucial ▪ Withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases.
CRP ≥ 100 mg/l
▪ Severe infection ▪ Prescribe antibiotics

The last section of the CRP training included two short video clips which showed the CRP test procedure, including how to take blood by using a finger prick, running the device and obtaining a result within 4 minutes. The training ends with a page summarising the key points of using point of care CRP testing in LRTI in primary care.

Appendix 2.

Table 5.- Characteristics of individual group (n (%) or mean (SD))

	Final twelve months follow-up				Initial three months follow-up period				Baseline
	Control	CRP	Communic'n	Both	Control	CRP	Commun'n	Both	
Gender (female)	730/1244 (59%)	736/1220 (60%)	740/1219 (61%)	884/1479 (60%)	553/870 (64%)	670/1062 (63%)	758/1170 (65%)	753/1162 (65%)	4218/6771 (62%)
Age in years (mean (SD))	50.6 (18.5)	51.8 (18.7)	52.8 (19.0)	50.8 (18.7)	50.5 (17.4)	51.1 (17.7)	51.3 (17.1)	50.9 (17.2)	49.6 (18.6)
Illness duration prior to the index consultation greater than 5 days	512/1244 (41%)	520/1220 (43%)	514/1219 (42%)	678/1479 (46%)	424/863 (49%)	570/1054 (54%)	614/1164 (53%)	558/1155 (48%)	3,542/6717 (53%)
Respiratory rate (> 25 breaths/min.)	39/1244 (3%)	57/1220 (5%)	26/1218 (2%)	76/1479 (5%)	63/846 (7%)	82/1020 (8%)	38/1030 (3%)	41/1145 (4%)	N/A
Temperature (higher than 38 degrees C)	165/1244 (13%)	120/1220 (10%)	126/1219 (10%)	260/1479 (18%)	96/849 (11%)	106/1004 (11%)	132/1153 (11%)	174/1148 (15%)	N/A

Table 6 - Comparison of characteristics of patients and antibiotic prescribing from practices which provided follow-up compared with overall cohort (n (%) or mean (SD)

	Final twelve months follow up	Initial three months follow up in those who provided twelve months follow up data	Initial three months follow up	Baseline
Gender (female)	2,891/4830 (59.8%)	2,112/3280 (64.39%)	2,734/4264 (64.1%)	4218/6771 (62%)
Age in years (mean (SD))	51.6 (18.8)	51.1 (17.6)	51.0 (17.4)	49.6 (18.6)
Non-smoker (past or current)	N/A	2561/3280 (78.1%)	3340/4264 (78.3%)	N/A
Illness duration prior to the index consultation greater than 5 days	2,097/4830 (43.4%)	1,649/3265 (50.5%)	2,166/4236 (51.1%)	3,542/6717 (53%)
Respiratory rate (greater than 25 breaths/minute)	178/4830 (3.7%)	184/3190 (5.8%)	224/4122 (5.42%)	N/A
Temperature (greater than 38 degrees C)	639/4830 (13.2%)	408/3235 (12.6%)	508/4154 (12.2%)	N/A
Sputum production	N/A	2631/3271 (80.4%)	3,448/4249 (81.2%)	5355/6771 (79%)
Percentage prescribed antibiotics at baseline	53.7%	55.5%	55.6%	55.3%

Appendix 3.

Factorial and Individual group results for LRTI and URTI subgroups

There was no significant difference between patients with LRTI and URTI (interaction term for antibiotic prescribing between RTI and CRP group 1.15 (p=0.569), and 1.51 (p=0.851) between RTI type and communication group) but since the power to assess interactions was limited the individual results for LRTI and other RTIs are shown below.

LRTI/URTI Factorial analysis

		Control for CRP	**CRP**		**Control for Communication**	**Communication**
LRTI						
Antibiotics Prescribed	Crude percentage	672/1293 (51.97%)	728/1424 (51.12%)		673/1217 (55.30%)	727/1500 (48.50%)
	Basic risk ratio	1.00	0.97 (0.89, 1.05; p=0.439)		1.00	0.94 (0.86, 1.00; p=0.074)
	Adjusted risk ratio	1.00	0.79 (0.59, 1.03; p=0.082)		1.00	0.75 (0.56, 0.97; p=0.024)
URTI						
Antibiotics Prescribed	Crude percentage	292/940 (31.06%)	265/923 (28.71%)		289/907 (31.86%)	268/956 (28.03%)
	Basic risk ratio	1.00	0.94 (0.81, 1.08; p=0.373)		1.00	0.94 (0.81, 1.09; p=0.445)
	Adjusted risk ratio	1.00	0.81 (0.57, 1.10; p=0.188)		1.00	0.83 (0.59, 1.12; p=0.232)

572
573 **LRTI/URTI Individual group analysis**
574

LRTI	Control	CRP	Enhanced communication	Combined
Crude percentage antibiotic prescribed	378/642 (58.88%)	295/575 (51.30%)	294/651 (45.16%)	433/849 (51.00%)
Basic risk ratio	1.00	0.86 (0.59, 1.13; p=0.333)	0.75 (0.50, 1.01; p=0.064)	0.72 (0.49, 0.98; p=0.036)
Adjusted risk ratio	1.00	0.76 (0.47, 1.06; p=0.112)	0.71 (0.45, 0.99; p=0.046)	0.59 (0.36, 0.86; p=0.003)
URTI	**Control**	**CRP**	**Enhanced communication**	**Combined**
Crude percentage antibiotic prescribed	180/486 (37.04%)	109/421 (25.89%)	112/454 (24.67%)	156/502 (31.08%)
Basic risk ratio	1.00	0.74 (0.48, 1.08; p=0.104)	0.75 (0.49, 1.08; p=0.138)	0.80 (0.53, 1.14; p=0.240)
Adjusted risk ratio	1.00	0.58 (0.36, 0.92; p=0.018)	0.60 (0.37, 0.94; p=0.023)	0.67 (0.42, 1.01; p=0.053)

575
576

577